Relapsed ALL: Does End-Induction MRD Predict 1 yr or 2 yr EFS ?

Intensive Induction Therapy for Children with Acute Lymphoblastic Leukemia who Experience a Bone Marrow Relapse: Results from COG Study AALL01P2

MRD as a Surrogate Endpoint Workshop

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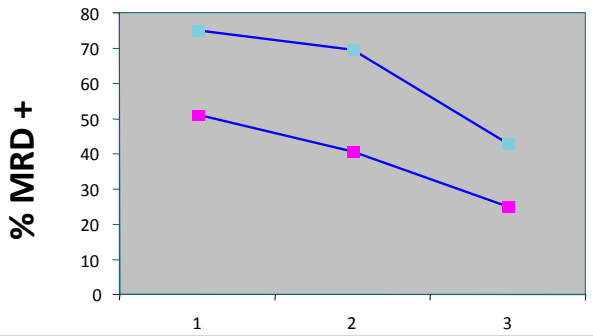
CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Introduction of New Agents at First Relapse

	Re-induction Block 1	Re-induction Block 2	Re-induction Block 3
COG: AALL01P2 1/03 -12/05 n=145	VCR, Pred, PEG, Doxo	CTX, Etop, MTX	ARA-C, ASP
	MRD, CR2		
COG: ADVL04P2 2/05-1/11 n=131	VCR, Pred, PEG, Doxo + epratuzumab	CTX, Etop, MTX	ARA-C, ASP
	MRD, CR2		



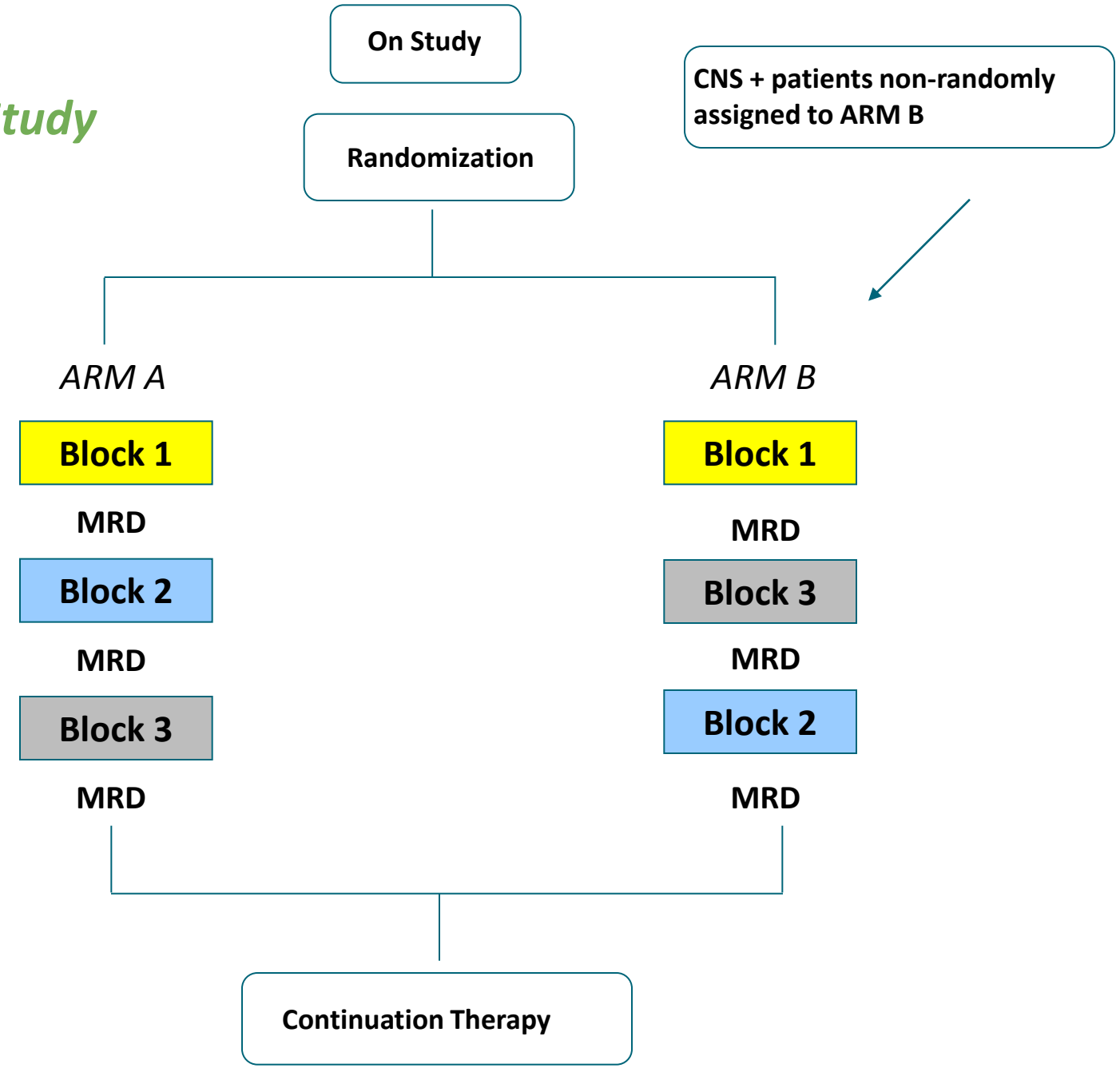
COG AALL01P2: Objectives and Eligibility

- Primary Aim
  - To develop a safe and active chemotherapy re-induction platform regimen for relapsed ALL, which could be used to evaluate novel agents in future trials
- Eligibility
  - Children 1-21 years of age with an initial ALL relapse involving the marrow (with or without associated extramedullary disease)

COG AALL01P2: Patient Characteristics

- Timing of Relapse
  - 69 Early relapse (< 36 months from diagnosis)
  - 55 Late relapse (≥ 36 months from diagnosis)
  - 4 Ph+
- Immunophenotype
  - 117 B lymphoblastic
  - 7 T-ALL
- Sites of Disease
  - 110 Isolated marrow, or marrow + other non-CNS EM site
  - 14 Marrow + CNS

AALL01P2 Study Design



COG AALL01P2: Accrual

Accrual

- Study opened January 27, 2003
- Permanently closed December 30, 2005
- 124 eligible patients enrolled after first amendment/therapy modification

COG AALL01P2: Remission Re-induction Rates

	Very Early Relapse (< 18 mo from dx)	*Early Relapse* (< 36 mo from dx)	*Late Relapse* (≥ 36 mo from dx)
All patients	45.0% ± 11.1% (n=24)	68.3% ± 5.9% (n=69)	96.3% ± 2.6% (n=55)
B-lineage, CNS-, Ph-	46.2% ± 13.8% (n=16)	72.0% ± 6.4% (n=55)	95.5% ± 3.1% (n=45)

Raetz et al. J Clin Oncol 2008 26:3971-3978

MRD Response Rates According to Timing of Relapse

	MRD Positive Patients * (%)	
Treatment Block	Early Relapse	Late Relapse
1	75 ± 7 (n = 36)	51 ± 8 (n = 43)
2	70 ± 10 (n = 23)	41 ± 4 (n = 32)
3	43 ± 11 (n = 21)	25 ± 8 (n = 28)

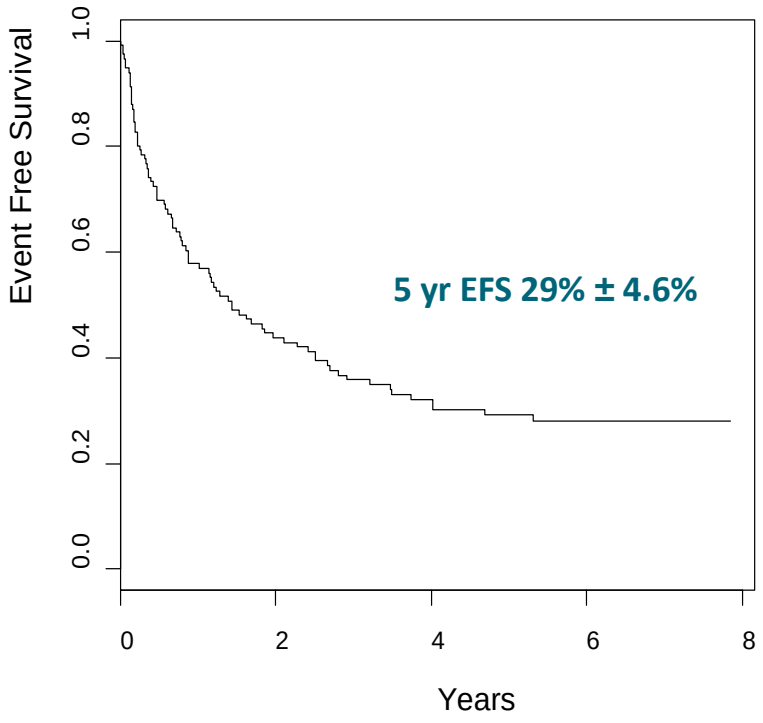
* All patients in complete remission at the end of block 1

At the end of three blocks of therapy, 16 (33%) of 49 of patients overall, remained MRD positive

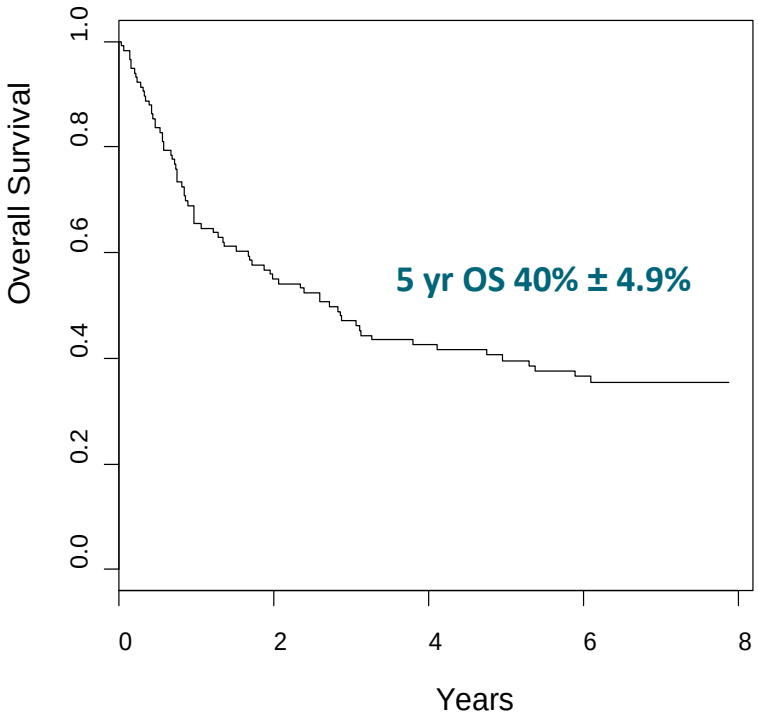
Raetz et al. J Clin Oncol 2008 26:3971-3978

COG AALL01P2: EFS and OS

All B Lymphoblastic Patients

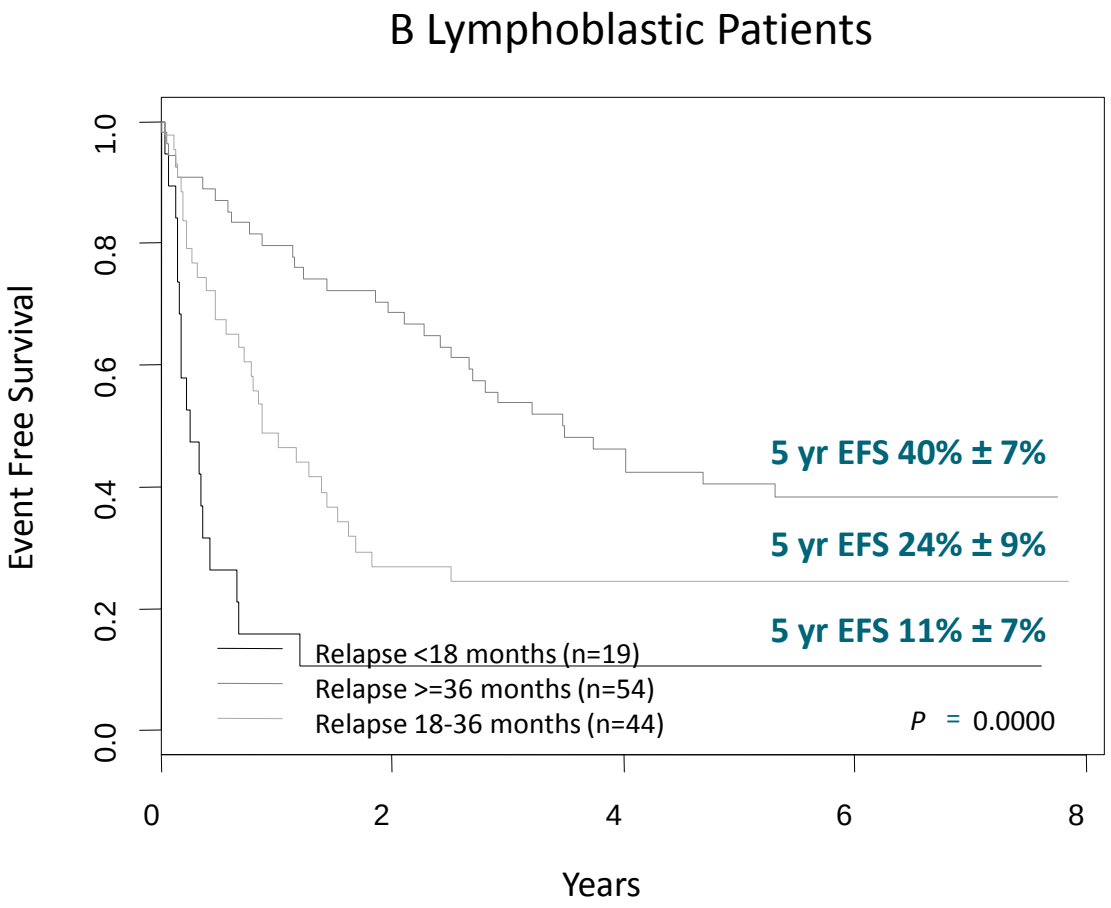


All B Lymphoblastic Patients



Data updated 2/24/12, Xiaomin Lu PhD

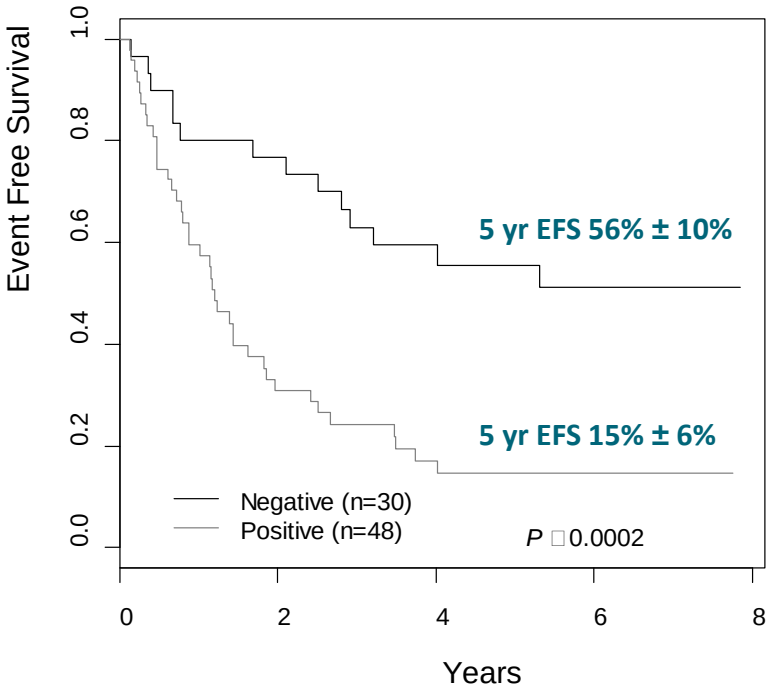
COG AALL01P2: Outcomes According to Time to Relapse



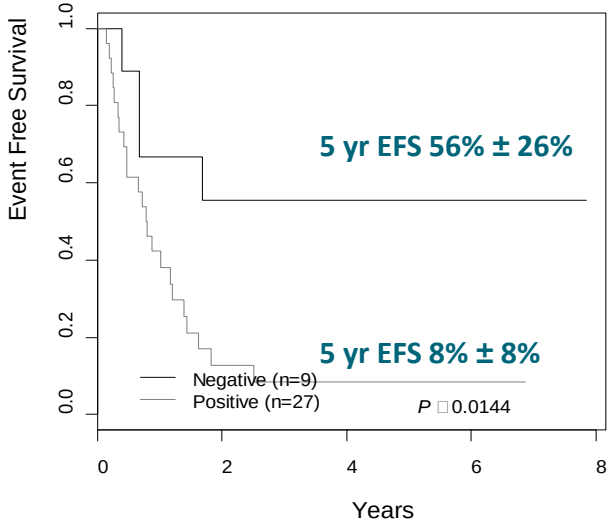
Data updated 2/24/12, Xiaomin Lu PhD

Outcomes According to Block 1 MRD Response

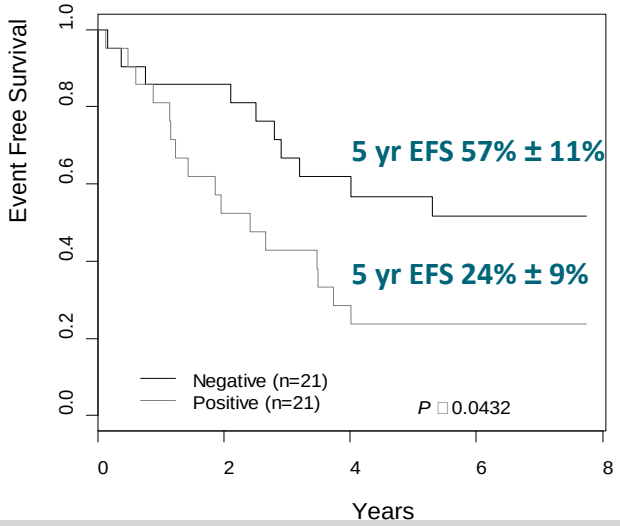
All B lymphoblastic patients with CR by MRD (0.01%)



Early relapse B lymphoblastic with CR by MRD (0.01%)

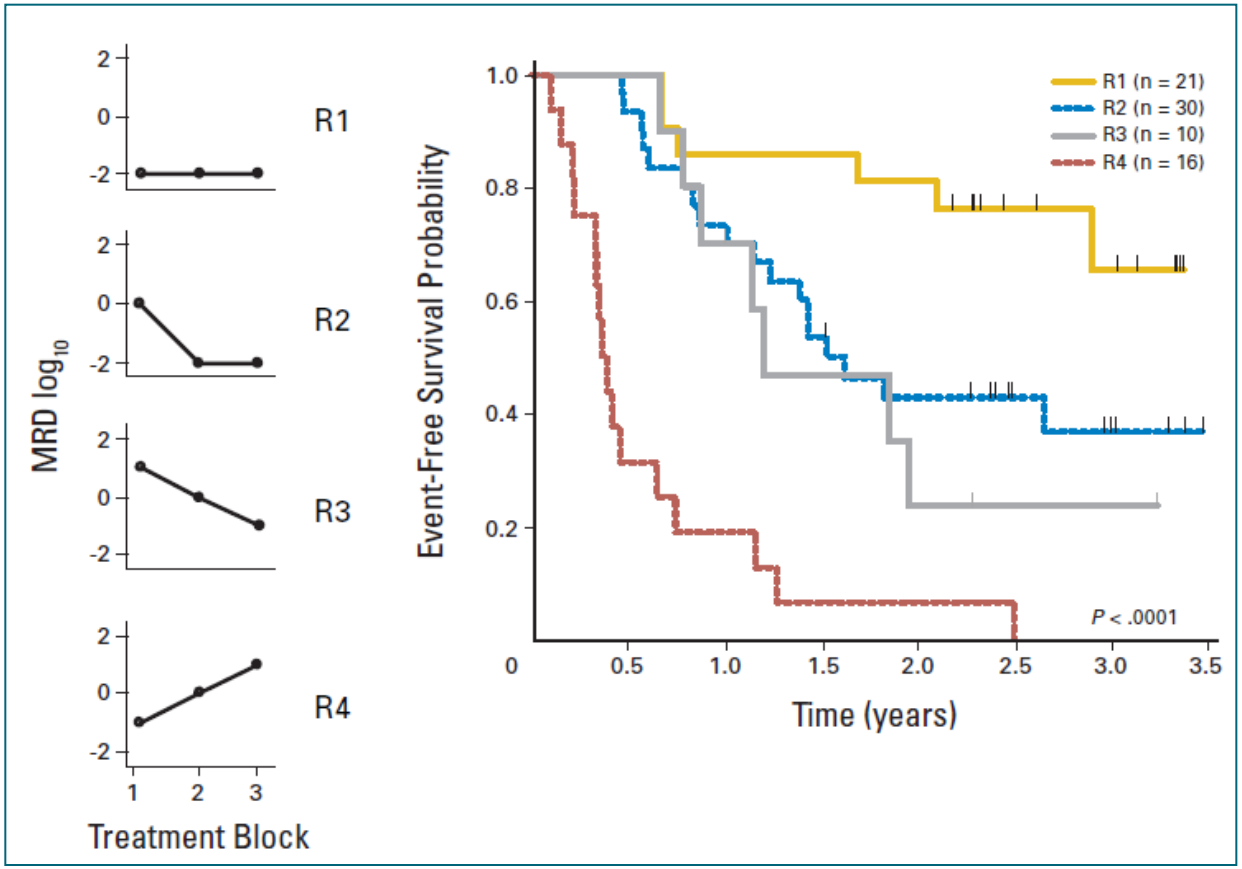


Late relapse B lymphoblastic with CR by MRD (0.01%)



Data updated 2/24/12, Xiaomin Lu PhD

Kinetics of MRD Response



~ 70% of patients who achieve CR2, but have detectable MRD at the end of block 1, will have sustained remissions and further reductions in MRD with ongoing therapy

Raetz et al. J Clin Oncol 2008 26:3971-3978

Reinduction Chemoimmunotherapy with Epratuzumab in Relapsed ALL in Children, Adolescents and Young Adults: COG Study ADVL04P2

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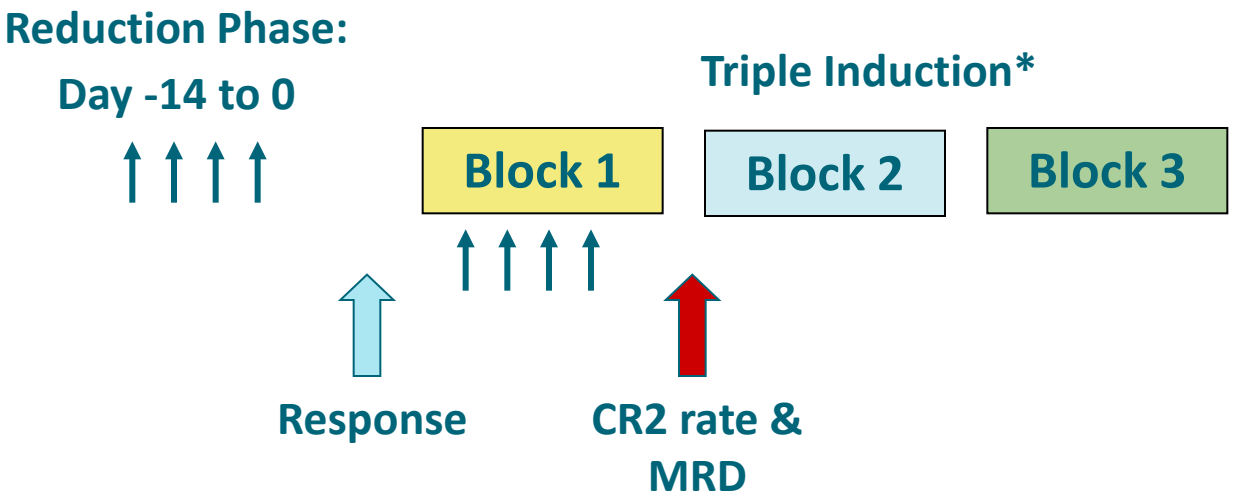
COG ADVL04P2: Objectives and Eligibility

- Primary Aim
  - To determine if addition of epratuzumab, an anti-CD22 monoclonal antibody, to the AALL01P2 backbone chemotherapy regimen improves rates of second complete remission (CR2) in children and young adults with ALL and early bone marrow relapse (<36 months from initial diagnosis)
- Eligibility
  - Children and young adults ages 2-30 years with first, early marrow relapse of CD22+ B-cell precursor ALL, with or without extramedullary disease

Study Design

Part A

Feasibility

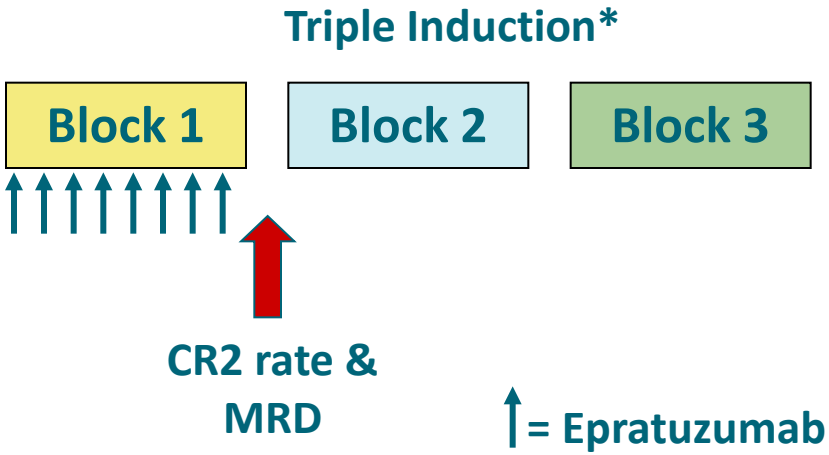


Part B

Phase 2 Pilot:

B1 Cohort

B2 Cohort



*COG AALL01P2; Raetz et al, JCO 2008 26:3971-8

Accrual

- Part A (Feasibility): Epratuzumab twice weekly x 4, then weekly x 4
  - 15 patients from 1/06-6/06
- Part B1 (Phase 2): Epratuzumab weekly x 4
  - 56 patients (54 eligible) from 1/07-12/08
- Part B2 (Phase 2): Epratuzumab twice weekly x 8
  - 60 patients from 1/09-1/11

Results Part A*: Reduction Phase and Block 1 Responses

Response	Number of Patients (n=15)
Reduction Phase	
• Stable Disease	8
• Minimal Remission Cytolytic	4
• Progressive Disease	3
End of Block 1	
• Complete Remission	9*
• Partial Remission (M2 marrow)	1
• Stable Disease	1
• Progressive Disease	1
• Died from infection or removed from protocol	3

**** Seven of nine patients achieving second CR had no detectable MRD***

*COG ADVL04P2; Raetz et al, JCO 2008 26:3756-62

Responses for B1 and B2 Cohorts

	B1 Cohort (weekly x 4)	B2 Cohort (twice weekly x 8)
Eligible Patients	54	60
Very Early Relapse (< 18mo)	23	19
Median Age at Relapse (yrs)	10.2	8.4
Extramedullary Disease	3	9
Response Evaluable Patients	48	50
End Block 1 CR2 Rate	65% (31/48)	66% (33/50)
End Block 1 MRD Available	31	31
End Block 1 MRD Neg (<0.01%)	45% (14/31)	39% (12/31)
End Block 1 MRD Neg Pooled	42% (26/62)*	

***Significantly higher than the 25% (9/36) with chemotherapy alone on AALL01P2 (one-sided p=0.001)**

Conclusions

- Rates of MRD positivity are much higher in relapsed ALL than newly diagnosed disease
- Early MRD response was a strong predictor for EFS on the COG AALL01P2 trial
- The kinetic pattern of MRD was also predictive of longer term outcomes in relapsed ALL on COG AALL01P2
- The combination of MRD response and timing of relapse identified different risk groups of patients, suggesting that MRD may be helpful in stratifying salvage therapy

Acknowledgements

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